



SITEMAN CANCER CENTER®

BARNES-JEWISH HOSPITAL • WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

A National Cancer Institute Comprehensive Cancer Center



A Phase I/II Trial of Stereotactic Body Radiation Therapy (SBRT) Dose Escalation in the Treatment of Patients with Inoperable Stage I/II Non-Small Cell Lung Cancer Arising within the Zone of the Proximal Bronchial Tree

HRPO #: 06-0691 / 201012832

Version date: 04/19/19

Principal Investigator

Clifford G. Robinson, M.D.
Department of Radiation Oncology
4921 Parkview Place
Campus Box 8224
Saint Louis, MO 63110
Telephone: 314-362-4633
Fax: 314-747-9557
crobinson@radonc.wustl.edu

Sub-Investigators

Jeffrey D. Bradley, M.D.
Department of Radiation Oncology
4921 Parkview Place
Campus Box 8224
Saint Louis, MO 63110
Telephone: 314-362-4633
Fax: 314-747-9557
jbradley@radonc.wustl.edu

Statistician

Feng Gao, M.D., Ph.D.
Department of Surgery
600 S. Taylor Ave.
Campus Box 8100
Saint Louis, MO 63110
Telephone: 314-362-3682
feng@wustl.edu

SCHEMA

Phase I

**R
E
G
I
S
T
E
R**

Stereotactic Body Radiation Therapy
(SBRT), 5 fractions over 2-3 weeks

Dose Level A – 9 Gy x 5*

Dose Level B – 10 Gy x 5*

Dose Level C – 11 Gy x 5*

Dose Level D – 12 Gy x 5*

Phase II

Deliver maximum tolerated dose from Phase I portion to 43 patients with the objective of determining local control rate (primary objective) and patterns of recurrence disease-free and overall survival rates (secondary objectives) at two years.

* Biological equivalent dose (BED) levels: A – 85.5 Gy; B- 100 Gy; C- 115.5 Gy; D- 132 Gy. $BED = nd(1 + d/\alpha/\beta)$ where n =number of fractions , d =daily dose, and $\alpha/\beta = 10$ for tumors.

Patient Population: (See Section 3.0 for eligibility)

Patients with T1, T2 (≤ 7 cm), or T3 (≤ 7 cm), N0, M0 (stage I or II) medically inoperable non-small cell lung cancer involving the central chest. Patients with tumors ≤ 7 cm that are invading or abutting the mediastinal pleura or parietal pericardium, including those tumors located within the *zone of the proximal bronchial tree* are eligible. (See Figure 1)

TABLE OF CONTENTS

SCHEMA	1
1.0 INTRODUCTION	4
1.1 Stage I Non-small Cell Lung Cancer.....	4
1.2 Stereotactic Body Radiation Therapy	5
1.3 Rationale for Proposed SBRT Dose Schema	8
1.4 Summary of Phase I Results for this trial	11
2.0 OBJECTIVES	12
3.0 ELIGIBILITY.....	12
4.0 REGISTRATION.....	14
4.1 Confirmation of Patient Eligibility	14
4.2 Patient Registration in the Siteman Cancer Center Database.....	14
4.3 Assignment of UPN.....	14
5.0 RADIATION THERAPY	14
5.1 Dose Specifications.....	14
5.2 Technical Factors	16
5.3 Localization, Simulation, and Immobilization	16
5.4 Treatment Planning/Target Volumes	17
6.0 CRITICAL STRUCTURES.....	20
6.1 Critical Organ Dose-Volume Limits.....	20
6.2 Contouring of Normal Tissue Structures	21
7.0 DOCUMENTATION REQUIREMENTS.....	22
7.1 Treatment Breaks.....	22
8.0 COMPLIANCE CRITERIA	22
8.1 Dosimetry Compliance	22
8.2 Treatment Delivery Compliance.....	22
9.0 RADIATION TOXICITY	23
9.1 Radiation Pneumonitis	23
9.2 Bronchial Injury	23
9.3 Other Significant Toxicity	24
10.0 STUDY CALENDAR.....	24
11.0 DATA SUBMISSION SCHEDULE.....	25
12.0 CRITERIA FOR EVALUATION	25
12.1 Baseline documentation of “Target” and “Non-Target” Lesions.....	25
12.2 Criteria for Removal from Protocol Treatment	26
13.0 ADVERSE EVENT REPORTING	27
13.1 Adverse Events (AEs).....	27
13.2 Unanticipated Problems	27
13.3 Noncompliance	27
13.4 Serious Noncompliance	28
13.5 Reporting to the Human Research Protection Office (HRPO) and the Quality Assurance and Safety Monitoring Committee (QASMC):.....	28
13.6 Reporting of AE Information Following Study Completion	28
13.7 SBRT Adverse Event Reporting	28
13.8 Life-Threatening, Grade 4, and Grade 5 Events.....	30
14.0 DATA AND SAFETY MONITORING	30
15.0 STATISTICAL CONSIDERATIONS	31
15.1 Statistical Methods for Phase I Portion	31
15.2 Statistical Methods for Phase II Portion	33
15.3 Monitoring the Study for Early Stopping Due to Unacceptable Toxicity	34
15.4 Accrual	34
15.5 Interim Analysis.....	34
16.0 REFERENCES	35

1.0 INTRODUCTION

1.1 Stage I Non-small Cell Lung Cancer

Lung cancer is the most frequent cause of cancer death in both men and women in North America, accounting for approximately 13% of all cancers diagnosed and 28% of all cancer deaths. There will be an estimated 173,770 new lung cancer cases in the United States in the year 2004 with an estimated 160,440 deaths due to lung cancer.¹ Seventy-five percent of patients with bronchogenic carcinoma will be diagnosed with non-small cell lung cancer (NSCLC). The number of patients with early or localized disease (currently an estimated 15-20% of NSCLC patients)² is expected to rise over the next several years due to widespread screening with CT scanning.

The treatment of choice for stage I (T1-T2N0) NSCLC is surgical resection which results in 5-year survival rates of approximately 60 to 70%.³⁻⁵ Occasionally, however, there are patients with early-stage NSCLC that are unable to tolerate surgical resection or the postoperative recovery period due to various comorbidities.

While conventionally fractionated radiation therapy has been utilized as nonsurgical therapy for these medically inoperable patients, close observation with no specific cancer therapy has also been advocated in highly selected cases. McGarry, et. al., reviewed outcomes in 75 patients who had received no specific cancer therapy for stage I NSCLC, and the cause of death was progressive cancer in 53% of cases with a median survival time of 14.2 ± 2.4 months.⁶

Definitive conventionally fractionated RT for early-stage NSCLC is considered reasonable non-surgical therapy but yields poor 5-year survival rates ranging from 10 to 30%.⁷⁻¹¹ Several studies have suggested a dose-response relationship reporting a benefit to dose escalation above the standard conventionally fractionated 4,500 to 6,600 cGy. This benefit was evident in both survival and local control in these patients.¹⁰⁻¹⁴ Sibley, et. al., reviewed 156 medically inoperable patients with stage I NSCLC treated with primary RT at Duke University between 1980 and 1995. They reported a 5-year, cause-specific survival rate of 32%. There was a trend toward improved survival in those patients achieving local control which approached significance for higher RT doses ($p = 0.07$).¹³ At this institution, we have published a series treating 56 patients with medically inoperable NSCLC with a median dose of 70 Gy using conformal radiotherapy techniques.¹⁵ Actuarial local control rates were 69% and 63% at two- and three years of follow up, respectively. These data serve as the estimate for statistical power calculations for this trial.

Radiation fields have historically encompassed the primary tumor as well as the regional lymphatics in the ipsilateral hilum and mediastinum. This elective treatment was based on the identified risk of occult lymph node involvement ranging up to 20% in some surgical series.¹⁶ In recent years, elimination of elective nodal irradiation, which is potentially poorly tolerated in this population,¹⁷ has been validated by several retrospective studies permitting treatment of the primary tumor alone with limited fields.¹⁸⁻²¹ Slotman, et. al., in a study from the Netherlands, reported the use of limited "postage-stamp" fields to treat early stage lung cancer patients using hypofractionated RT (*i.e.*, 4,800 cGy in 400-cGy fractions). Reported 3-year overall and disease-specific survival rates were 42% and 76%, respectively.²⁰

Most of the aforementioned retrospective studies utilized radiotherapy equipment from the era of 1-D and 2-D treatment planning. Several limitations are evident from these older techniques, including target visualization, selection of beam directions, and computational algorithms describing deposited dose. Recent improvements in software, hardware, and computer processing speed have revolutionized the delivery of radiation doses appropriate for tumor cell killing.

In this new era of three-dimensional treatment planning, more precise delivery methods are available allowing for dose escalation to the target volume without excessive dose being deposited in normal tissues. The RTOG has completed an extensive dose escalation study of conventionally fractionated three-dimensional conformal radiotherapy (3D-CRT) for NSCLC for stages I, II, and III disease as long as all detectable tumor can be encompassed by the radiation therapy fields including both primary tumor and regional lymph nodes.²² No mechanism for minimizing lung and tumor movements was utilized. One hundred and seventy-nine patients were treated with radiation doses escalated to as high as 90.3 Gy. Patients were stratified within each dose level according to the percentage of the total lung volume that received >20 Gy with the treatment plan (V_{20}). For patients receiving radiation alone or radiation following induction chemotherapy, data from RTOG 9311 established that the radiation dose could be safely escalated using 3D-CRT techniques to 83.8 Gy for patients with V_{20} values of <25% and to 77.4 Gy for patients with V_{20} values between 25% and 36%, using fraction sizes of 2.15 Gy. Excess mortality was observed at 90.3 Gy with two dose-related deaths. The incidence of grade 3 or higher acute toxicity is less than 10%; however, grade 3 or higher late toxicity was approximately 15%.

1.2 Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is the delivery of high precision, biologically potent doses of radiation to tumors of the chest,

abdomen, and pelvis. Implementing elements of 3D-CRT with stereotactic targeting, SBRT permits delivery of 3-4 high dose fractions totaling 48-60 Gy with good local control and low toxicity.

Blomgren, et. al., from the Karolinska Hospital in Stockholm, Sweden reported the results of over 100 patients treated in the extracranial stereotactic frame (developed by researchers at the Karolinska Hospital) for metastases in the chest and abdomen beginning in 1992.^{23, 24} More recently, Blomgren, et. al., reported the treatment of 17 patients with extracranial stereotactic radiotherapy for lung metastases.²⁵ Tumors ranged from 1.8 cm to 7.2 cm in size. Margin doses ranged from 20 Gy in a single fraction to 45 Gy in three fractions. Follow-up ranged from 3.5 to 25 months. Repeat CT scans to assess response to treatment demonstrated disappearance in 35%, reduction in 41%, stabilization in 18%, and progression in only one patient (the largest tumor treated in the report). Because of concern for acute inflammatory effects, all patients were pre-medicated with corticosteroids prior to treatment. Side effects were, however, limited and primarily consisted of fatigue and fever for a few days after the treatments. One patient experienced typical radiation pneumonitis two months after treatment, with subsequent fibrosis, and another developed a chronic cough. There was no severe late pulmonary toxicity or treatment-related deaths.

A phase I dose escalation trial has been completed at Indiana University for treatment of medically inoperable patients with stage I NSCLC.^{26, 27} SBRT was administered with large doses per fraction in an extracranial stereotactic body frame, which includes a system for decreasing breathing motion. The starting dose was 8 Gy times 3 (24 Gy total), and fraction dose was escalated by 2 Gy per fraction for each cohort. The target lesion was outlined by a physician and designated as the gross tumor volume (GTV). An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane was added to the GTV to constitute the PTV based on validation measurements for this commercially available system.^{23, 28, 29} Typically, 7 to 10 non-coplanar beams were used to encompass the PTV. Dose was prescribed to the 80% isodose line. However, higher isodoses occurred within the center of the target mimicking the heterogeneous dose profile common to intracranial stereotactic radiosurgery. The treatment isocenter was identified with 3-D coordinates defined stereotactically and localized on verniers attached to the frame. No skin or bony landmarks were used to set the treatment isocenter; however, orthogonal port films were used on a daily basis for isocenter verification.³⁰ Separate dose escalations were carried out independently for patients with T1 versus T2 small (≤ 5 cm) versus T2 large (5-7 cm) tumors at diagnosis.

According to the Indiana University protocol guidelines, dose-limiting toxicity (DLT) was any grade 3 cardiac or pulmonary toxicity or any grade

4 toxicity attributed to the therapy. Thirty-seven patients were treated using a standard dose escalation protocol with 3 patient cohorts with minimum 1 month between dose levels to assess toxicity. Patients were categorized into separate independent dose escalations according to tumor volume, T1 vs. T2 (≤ 5 cm) vs. T2 (> 5 to ≤ 7 cm). Grade 3 pneumonitis was seen at a dose of $14 \times 3 = 42$ Gy total in one T2 patient with a 7-cm tumor and transient grade 3 hypoxia was seen at $16 \times 3 = 48$ Gy total in one patient. Additional patients were treated at each of these levels without further toxicity observed. Twenty-one patients had mild to moderate fibrosis distal to the treated lesion appear on chest x-ray after treatment. Nine of these patients had a decline of an element of their pulmonary function tests (FEV1, FVC, DLCO, or PO2) by 10-20% of predicted which returned back to baseline values with follow-up in all but two. The timing of onset of this toxicity was generally acute to subacute (< 1 month in most cases). The maximum tolerated dose (MTD) was not reached on this trial for patients with T1 tumors and smaller T2 tumors (≤ 5 cm). Dose-limiting pneumonitis or pericarditis occurred in 2/5 patients with larger T2 tumors (>5 to ≤ 7 cm) at a dose of $24 \times 3 = 72$ Gy defining the MTD for this subgroup at $22 \times 3 = 66$ Gy. Patients treated at a dose of 22 Gy per fraction times three fractions had follow up of over 24 months without late toxicity for all T-stage tumor categories. Treatment failure within the PTV has been observed in 8 of 26 patients treated at doses of up to $20 \times 3 = 60$ Gy. However, all but one of these local failures occurred at doses of $16 \times 3 = 48$ Gy or lower.³¹

Onishi, et. al., showed that patients treated with biologically effective doses (BED) of ≥ 100 Gy [using $BED = nd(1 + d/\alpha/\beta)$, where n = number of fractions, d = dose per fraction, and $\alpha/\beta = 10$ for acute-reacting tissue] had better local control and survival compared to those receiving BED < 100 Gy. Local recurrence rates were significantly lower for tumors treated with BED ≥ 100 Gy (8.1% vs. 26.4%, $p < 0.01$). The 3-year overall survival rate of medically operable patients was 88.4% for BED ≥ 100 Gy compared with 69.4% for BED < 100 Gy. Though not all agree, these data are consistent with other reports in the literature supporting the use of BED values greater than 100 Gy for optimal local control of lung tumors with SBRT.^{32, 33}

The above data demonstrate that solitary lung lesions including early stage NSCLC are better controlled with SBRT when compared to conventional radiation. In addition, reduced volume treatments are attractive in these patients with medically inoperable stage I NSCLC who may have an increased risk of radiation pneumonitis associated with conventional large volume radiation fields. SBRT permits dose escalation by significantly reducing the high-dose treatment volume.

The RTOG opened in May 2004 a phase II trial of SBRT in the treatment

of medically inoperable patients with stage I/II non-small cell lung cancer in an effort to determine if SBRT could achieve acceptable local control as seen in retrospective series.^{24, 26, 32-38} A secondary objective is to determine if this technique achieves acceptable treatment-related toxicity. In this trial, patients with T1, T2 (≤ 5 cm), or T3 (≤ 5 cm), N0, M0 medically inoperable non-small cell lung cancer are treated with SBRT to a total of 60 Gy in 3 fractions of 20 Gy each over 1.5 to 2 weeks. This protocol excludes patients with T3 tumors involving the central chest and structures of the mediastinum as well as patients with any T-stage tumor within or touching the zone of the proximal bronchial tree. This region is defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, and right and left lower lobe bronchi). See figure below:

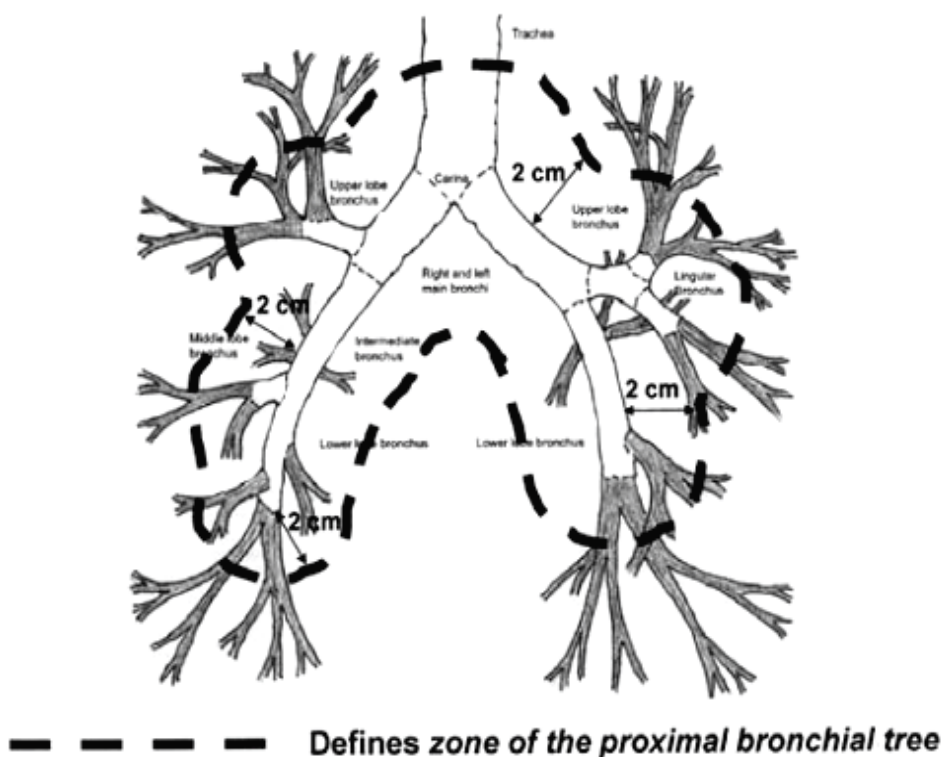


Figure 1.0

1.3 Rationale for Proposed SBRT Dose Schema

Because the proximal bronchial tree functions more as a serial organ similar to the hollow viscera (e.g. GI tract) as opposed to the periphery of the lungs which function in parallel with inherent redundancy, focal radiation injury to the central lung structures such as the bronchi can theoretically adversely affect the distal parenchyma. For this reason and because of their proximity to large blood vessels, central lung tumors have been excluded from most SBRT trials. The tolerance of the bronchial tree

to SBRT is unknown. Investigators at the University of Colorado have treated patients with central lung lesions on their SBRT trials without adverse consequences. Doses of 60 Gy delivered in 3 fractions of 20 Gy each were tolerated by the primary or secondary bronchi (unpublished data). Onishi and colleagues made no effort to restrict the location of eligible tumors, irrespective of whether they were located adjacent to a major bronchus or blood vessel. Seventeen patients (6.9%) experienced symptomatic radiation-induced pulmonary toxicity (grade >1), 88% of which had pulmonary fibrosis or emphysema prior to SBRT. Pulmonary symptoms resolved in most patients with or without steroid therapy. No vascular or cardiac complications were encountered.³² Uno and colleagues have reported a case of chronic radiation bronchitis in a 73 year old woman with medically inoperable T1N0M0 adenocarcinoma of the lung which developed as a severe cough 6 months after treatment with SBRT to 50 Gy in 5 fractions of 10 Gy each. Fiberoptic bronchoscopy revealed thick circumferentially coated bronchial mucosa in a segmental bronchus which was located within the 90% dose area. A follow-up bronchoscopy at 12 months confirmed marked stenosis in the segmental bronchus without tumor progression.³⁹

The efficacy and safety of endobronchial brachytherapy (EBBT) in which high doses per fraction are delivered to the bronchi from within have been well established in the literature. This well-tolerated procedure delivers very high doses of radiation to the bronchial mucosa with a low complication rate and provides a high likelihood for durable palliation of symptoms that are associated with endobronchial tumors. Given the paucity of data evaluating the toxicity of SBRT for central lung tumors, a crude comparison with EBBT is reasonable.

Speiser and Spratling described radiation bronchitis and stenosis secondary to high dose rate endobronchial irradiation which occurred in 12% of patients.^{40, 41} The complication rate increased slightly with concurrent external beam radiation therapy, curative intent, prior laser photoresection, and/or large cell histology. There was no significant difference in complication rate between the three study groups receiving 10 Gy at 5 mm depth via medium dose rate EBBT for three fractions, 10 Gy at 10 mm depth via high dose rate EBBT for three fractions, or 7.5 Gy at 10 mm depth via high dose rate EBBT for three fractions. Radiation bronchitis and stenosis (RBS) was defined in this study as a spectrum of clinical changes which occurred in the tracheobronchial tree as seen on follow-up bronchoscopy 6 weeks after the EBBT treatment. Higher grade (grade 3 and 4) RBS was characterized by a severe inflammatory response with marked membranous exudates and mild to severe fibrosis/stenosis requiring various interventions to re-establish the full lumen of the airway. This degree of late toxicity developed in 6% of patients with means of 43 and 55 weeks for grade 3 and 4, respectively.

Intervention was typically more aggressive and difficult for grade 4 reactions because of the circumferential fibrosis leading to progressive reduction in the luminal diameter of the bronchus. Fatal hemoptysis occurred with an overall rate of 7.3%. In all cases, patients dying of massive hemoptysis had residual or recurrent carcinoma seen on bronchoscopy, post-mortem exam, and/or radiographic studies. There were no proven cases of necrosis into the pulmonary artery in the absence of residual or recurrent carcinoma.

M. D. Anderson has reported their ten-year experience with EBBT. Most patients received 3,000 cGy via EBBT delivered to a depth of 6 mm and divided into 2 fractions of 1500 cGy each over 2 weeks. Complications occurred in 19 out of 175 treated patients (11% crude rate) with an actuarial complication rate of 13% at 1 year from the time of the first EBBT treatment session. The most significant associated toxicity was late massive hemoptysis, which occurred in this study with an actuarial hazard ratio of 5%.⁴²

Celebioglu, et. al., have reported a very low complication rate in their published experience of 95 patients with inoperable endobronchial lung tumors treated with either 7.5 Gy times three one week apart or 10 Gy times two one week apart. Endobronchial irradiation was delivered to a 1.0-cm depth using remote afterloading high dose rate brachytherapy with iridium-192. Sixty patients (63%) had previously received large field external beam radiotherapy (EBRT) to 46 Gy. Estimated BED for acute-reacting tissues ($\alpha/\beta = 10$) was 40 Gy for EBBT and 55.2 Gy for EBRT. One patient (1%) had hemoptysis in week 5 requiring hospitalization and it was relieved after symptomatic therapy. None of the patients experienced fistula or cardiovascular problems. Follow-up bronchoscopies revealed clinically insignificant radiation changes including dry mucosa with varying degrees of stenosis.⁴³

Though a direct comparison between EBBT and SBRT is not possible, the resilience of the proximal bronchial tree and nearby mediastinal structures to a high dose of radiation is clearly demonstrated. Because complications can be severe due to the proximity of vital structures, steps must be taken to optimize the delivery and fractionation of SBRT for central lung tumors in order to provide good local tumor control while minimizing toxicity.

Accurate and precise treatment planning and delivery methods should be employed in an effort to reduce the deleterious effects of setup error and organ motion. Deep inspiration breath-hold techniques and respiratory gated radiotherapy in which a beam-on mode is triggered by certain phases of the respiratory cycle are current topics of clinical research.^{44, 45} Others are studying a surrogate marker for tumor motion which is detected by a tracking system that allows the radiation source to follow the position

of the tumor.³⁸ Current studies report only the feasibility of these approaches. Clearly, however, SBRT relies heavily upon precise target localization. Therefore, methods to reduce or compensate for tumor motion are mandatory.

The availability of the most recent technological advances in adaptive image-guided radiotherapy provides the Siteman Cancer Center a unique environment to deliver SBRT and track its efficacy. Four-dimensional computed tomography (4D-CT) and Varian Real-time Position Monitor® (RPM) together allow for accurate monitoring of and compensation for individualized tumor movement. The Varian Trilogy® linear accelerator provides improved efficiency with online localization using the onboard cone-beam kV CT which will eliminate the need for a pretreatment CT simulation. Furthermore, the Trilogy has been developed specifically as a stereotactic radiotherapy treatment machine calibrated to a precision of within 0.5 mm and capable of delivering SBRT with a specific high dose rate 6 MV photon beam at up to 1000 MU/min. The fluoroscopic capabilities of the Onboard Imager® will provide additional confirmation of coverage of the tumor during normal breathing motion.

With the improved accuracy and efficiency of the above tools, evaluation of SBRT for central lung tumors is feasible and desirable. We, therefore, propose a dose escalation schema starting with doses that are considered safe but suboptimal for tumor control (i.e. BED approaching 100 Gy), and escalating the dose per fraction to reach more optimal BED values. In order to reduce the toxicity of this treatment, we feel it is logical to increase the number of fractions from the current RTOG protocol.

1.4 Summary of Phase I Results for this trial

Twenty-three patients with histologically-proven Stage I NSCLC with tumors located within 2 cm of the proximal bronchial tree have been enrolled on Phase I of this trial. The primary objective was to determine the maximum tolerated dose of SBRT to the proximal bronchial tree. SBRT consisted of 5 fractions of 9, 10, 11, and 12 Gy each on cohorts A, B, C, and D, respectively, over a total of 10-31 days. A minimum of 5 patients were enrolled per cohort and at least 3 months of minimum follow up were required prior to opening the next dose level to accrual.

The mean (range) of follow up duration for cohorts A (n=5), B (n=6), C (n=6), and D (n=5) are 22.9 (6-47), 25.3 (2-42), 17.3 (13-22), and 6.6 (1-11) months, respectively. Two additional patients recently completed therapy on cohort C and are awaiting their initial follow up. Two patients treated to 10 Gy x 5 fractions developed an unrelated grade 3 lung toxicity which resolved. There have been no protocol-related toxicities to date. The overall primary tumor control rate is 95.8%. One primary tumor failure

occurred within cohort A. No local failures have occurred thus within cohorts B, C, or D. Sixteen of 24 patients remain alive with a projected 3-year overall survival rate of 54.3%. Based on the outstanding local control achieved at 11 Gy per fraction for 5 fractions, we have chosen to proceed to Phase II of this trial.

2.0 OBJECTIVES

1. The primary objective of the Phase I portion of this study is to determine the maximum tolerated dose of stereotactic body radiation therapy (SBRT) to the trachea and proximal bronchial tree.
2. The primary objective of the phase II portion of this study is to determine if the MTD determined in Phase I achieves acceptable local control (i.e. >80%) for this medically inoperable population of patients with non-small cell lung cancer.
3. The secondary objective of Phase II is to estimate the rates of regional nodal recurrence, disseminated recurrence, disease-free and overall survival at two years.

3.0 ELIGIBILITY

1. Histologically confirmed non-small cell cancer by biopsy or cytology. Squamous cell carcinoma, adenocarcinoma, large cell carcinoma, bronchioalveolar carcinoma, or non-small cell carcinoma (not otherwise specified) are allowed.
2. Staging studies must identify patient as AJCC Stage I or II based on only 1 of following combinations of TNM staging:
 - a. T1, N0, M0
 - b. T2 (≤ 7 cm), N0, M0
 - c. T3 (≤ 7 cm), N0, M0
3. Primary tumor must be arising in one of the following central chest locations:
 - a. Within or touching the *zone of the proximal bronchial tree* (a volume 2cm in all directions around the proximal bronchial tree [carina, R & L main bronchi, R & L upper lobe bronchi, intermedius bronchus, R middle lobe bronchus, lingular bronchus, R & L lower lobe bronchi]) - see *Figure 1*
 - b. Adjacent to (within 5 mm) or invading the mediastinal pleura
 - c. Adjacent to (within 5 mm) or invading the parietal pericardium
4. To differentiate T3 lesions involving the mediastinal pleura from T4 lesions involving major vessels or organs, a chest MRI will be obtained. If any uncertainty remains, the patient will have four-dimensional CT scans (4DCT) in an effort to determine the degree of tumor motion. A freely mobile tumor during ventilation will be judged to be T3 disease.

5. Patients with hilar or mediastinal lymph nodes ≤ 1 cm and no abnormal hilar or mediastinal uptake on PET will be considered N0. Patients with >1 cm hilar or mediastinal lymph nodes on CT or abnormal PET (including suspicious but non-diagnostic uptake) may be eligible if directed tissue biopsy of all abnormally identified areas are negative for cancer.
6. Primary tumor must be technically resectable by an experienced thoracic cancer clinician, with a reasonable possibility of obtaining a gross total resection with negative margins (potentially curative resection, PCR). However, patients must have underlying physiological medical problems prohibiting PCR (i.e., problems with general anesthesia, the operation, the post-op recovery period, or removal of adjacent functioning lung) or refuse surgery. Deeming a patient medically inoperable based on pulmonary function for surgical resection may include any of the following: baseline FEV1 $<40\%$ predicted; post-operative predicted FEV1 $<30\%$ predicted; severely reduced diffusion capacity; baseline hypoxemia and/or hypercapnia; exercise oxygen consumption $<50\%$ predicted; severe pulmonary hypertension; diabetes with severe end organ damage; severe cerebral, cardiac, or peripheral vascular disease; or severe chronic heart disease. Any one of these problems will qualify a patient for this trial.
7. Age ≥ 18 .
8. Zubrod performance status 0-2.
9. Women of childbearing potential must use effective contraception.
10. No direct evidence of regional or distant metastases after appropriate staging studies. No synchronous primary or prior malignancy in past 2 years except non-melanoma skin cancer or *in situ* cancer.
11. No previous lung or mediastinal radiation therapy.
12. No plans for concomitant antineoplastic therapy (including standard fractionated RT, chemo, biologic, vaccine therapy, or surgery) while on this protocol except at disease progression.
13. No active systemic, pulmonary, or pericardial infection.
14. No pregnant or lactating women.
15. PRESTUDY REQUIREMENTS:
 - a. History and Physical Examination, Weight, Zubrod performance status (within 4 weeks pre-study entry)
 - b. Evaluation by thoracic cancer clinician (within 8 weeks pre-study entry)
 - c. Pregnancy test, if applicable (serum or urine, within 72 hours prior to treatment start.)
 - d. CT* (preferably with contrast unless medically contraindicated; both lungs, mediastinum, liver, adrenals)
 - e. PET* (using FDG with visualization of primary tumor and draining lymph node basins in hilar and mediastinal regions)
 - f. Brain MRI or head CT with contrast
 - g. PFTs - include routine spirometry, lung volumes, diffusion capacity
 - h. Signed informed consent.

4.0 REGISTRATION

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Database

All patients must be registered through the Siteman Cancer Center database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 RADIATION THERAPY

5.1 Dose Specifications

5.1.1 Stereotactic Targeting and Treatment

The term "stereotactic" for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of

radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. This differs from conventional radiation therapy in which therapy is directed toward skin marks or bony landmarks that are indirectly referenced to the tumor. This known 3D coordinate system may include external fiducial markers (i.e. Elekta body frame), internal fiducial markers (i.e. gold seeds), or image-guided systems using either on-board kV or cone beam CT imaging (i.e. Varian Trilogy linear accelerator).

5.1.2 Dose Fractionation

Patients will receive 5 fractions of radiation according to Table 1. The dose for all patients will be 9 to 12 Gy per fraction to the prescription line at the edge of the PTV, depending on the dose level assigned for the patient.

Table 1: Phase I Dose Escalation Scheme

Dose Level	Fractionation	Biological Equivalent Tumor Dose
1	9 Gy x 5 fractions	85.5 Gy
2	10 Gy x 5 fractions	100 Gy
3	11 Gy x 5 fractions	115.5 Gy
4	12 Gy x 5 fractions	132 Gy

* Each patient must have a minimum follow up period of 3 months prior to proceeding to the next dose level. After completing accrual to dose levels 2 and 3 (during the 3 month assessment window) accrual to the trial may continue at the previous 'safe' dose level. For example, if dose level 1 proves safe, patients can be accrued and treated at dose level 1 during the 3 month window of toxicity assessment between dose levels 2 and 3.

5.1.3 Premedications

Unless contraindicated, it is recommended that all patients receive corticosteroid premedication (e.g. Decadron 4 mg p.o. in a single dose, or equivalent) 15-60 minutes prior to each of the three treatments for the intended purpose of modulating immediate pulmonary inflammatory effects. Analgesic premedication to avoid general discomfort during long treatment durations also is recommended when appropriate.

5.2 Technical Factors

5.2.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators are allowed. Photon beams with energies of 6 MV are preferred. Photon beam energies greater than 10 MV but not more than 15 MV will only be allowed for a limited number (≤ 2) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter.

5.2.2 Minimum Field Aperture (Field Size) Dimension

Due to uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, a minimum field dimension of 3.5 cm is required for any field used for treatment delivery. It is understood that this may exceed the technical requirements listed in Section 5.4 for small lesions (< 2.5 cm axial GTV dimension or < 1.5 cm cranio-caudal GTV dimension). In such cases, the prescription dose is still prescribed to the edge of the defined PTV.

5.2.3 Dose Verification at Treatment

Personal dosimeter measurements (e.g. diode, TLD, etc.) must be obtained for surface dose verification for accessible beams for the first fraction.

5.3 Localization, Simulation, and Immobilization

5.3.1 Patient Positioning

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 5.4 with any significant probability (i.e., $< 5\%$).

5.3.2 Inhibition of Effects of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (i.e. breathing, etc.) on target positioning and reproducibility. Acceptable maneuvers including reliable abdominal compression and accelerator beam gating with the respiratory cycle.

5.3.3 Localization

Daily CT localization of the GTV isocenter is required prior to each fraction. The process is as follows: A limited CT scan designed to encompass the GTV will be obtained. The GTV will be contoured by the treating physician and the isocenter coordinates of that volume determined. These x, y, and z coordinates will be used to set up the patient for stereotactic therapy. If the patient requires transfer from the CT couch to the treatment couch, isocenter localization images (anterior/posterior and lateral) should be obtained prior to each treatment on the treatment unit to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields.

5.4 Treatment Planning/Target Volumes

5.4.1 Image Acquisition

Computed Tomography (CT) using four-dimensional imaging techniques will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting and must be done with IV contrast, unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between tumor and adjacent vessels or atelectasis. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape. The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using CT pulmonary windows. However, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. **This target will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, only include abnormal CT signal consistent with gross tumor (i.e., the GTV and the Clinical Target Volume, CTV, are**

identical). An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (cranio-caudal) will be added to the GTV to constitute the planning treatment volume (PTV). These margins will be used at all sites, even if a particular site uses equipment or techniques felt to be more accurate.

5.4.2 Dosimetry

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, noncoplanar beams are preferable. Typically, 7-10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 7 non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e. no additional "margin" for dose build up at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3.5 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates may be determined either from fiducial markers or directly from the tumor using image-guidance and translated to the treatment record. The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COMPTV). Typically, this point will be the isocenter of the beam rotation. However, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COMPTV must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning – typically around 80%, but ranging from 60-90%. The prescription dose ranging from 45 to 60 Gy in five fractions (per patient dose assignment) will be delivered to the margin of the PTV and fulfill the requirements below. As such, a "hot spot" will exist within the PTV centrally at the COMPTV.

For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body, including lung, will be corrected for tissue heterogeneity.

Successful treatment planning will require accomplishment of all of the following criteria:

1. Normalization – The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COMPTV). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams.
2. Prescription Isodose Surface Coverage – The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (i.e., 9 Gy per fraction x 5 fractions = 45 Gy total), and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (i.e., 8.1 Gy per fraction = 40.5 Gy total).
3. Target Dose Heterogeneity – The prescription isodose surface selected in number 2 (above) must be $\geq 60\%$ of the dose at the center of mass of the PTV (COMPTV) and $\leq 90\%$ of the dose at the center of mass of the PTV (COMPTV). The COMPTV corresponds to the normalization point (100%) of the plan as noted in 1) above.
4. High Dose Spillage
 - a. *Location* - Any dose greater than 105% of the prescription dose (i.e., > 9.45 Gy per fraction = 47.25 Gy total for dose level 1) should occur primarily within the PTV itself and not within the normal tissues outside of the PTV. Therefore, the cumulative volume of all tissue outside of the PTV receiving a dose greater than 105% of prescription dose (>9.45 Gy per fraction = 47.25 Gy total) should be no more than 15% of the PTV volume.
 - b. *Volume* - Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1) through 4) to the volume of the PTV is ideally < 1.2 (See table below). These criteria will *not* be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) where the required minimum field size of 3.5 cm (see Section 5.4.2) results in the inability to meet a conformality ratio of 1.2.

5. Low Dose Spillage - The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
 - a. *Location* - The maximum total dose over all 5 fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction be no greater than D2cm where D2cm is given by the table below.
 - b. *Volume* - The ratio of the volume of 50% of the prescription dose (4.5Gy per fraction = 22.5 Gy total) isodose to the volume of the PTV must be no greater than R50% where R50% is given by the table below.

Table 2

Maximum PTV Dimension (cm)	Ratio of Prescription Isodose Volume to the PTV		Ratio of 50% Prescription Isodose Volume to the PTV, R _{50%}		Percent of Lung receiving 20 Gy total or more, V ₂₀ (%)		PTV Volume (cc)
	Deviation		Deviation		Deviation		
	none	minor	None	minor	none	minor	
2.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<10	10-15	1.8
2.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<10	10-15	3.8
3.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<10	10-15	7.4
3.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<10	10-15	13.2
4.0	<1.2	1.2-1.4	<3.8	3.8-4.0	<10	10-15	21.9
4.5	<1.2	1.2-1.4	<3.7	3.7-3.9	<10	10-15	33.8
5.0	<1.2	1.2-1.4	<3.6	3.6-3.8	<10	10-15	49.6

6.0 CRITICAL STRUCTURES

6.1 Critical Organ Dose-Volume Limits

The following table lists the guidelines for maximum dose to a point or volume within several critical organs. **The spinal cord limit is an absolute limit, and treatment delivery that exceeds this limit will constitute a major protocol violation.** The dose is listed as total over 5 fractions and per fraction. In order to verify each of these doses, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow.

Table 3—Critical Dose Guidelines

Organ	Volume	Dose (Gy)
Spinal Cord	Any point	20 Gy (4 Gy per fraction)
Esophagus	Any point	30 Gy (6 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	25 Gy (5 Gy per fraction)
Heart	Any point	50Gy (10 Gy per fraction)
Heart	<15 cc	<32 Gy (6.4 Gy per fraction)

6.2 Contouring of Normal Tissue Structures

6.2.1 Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

6.2.2 Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

6.2.3 Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

6.2.4 Proximal Trachea

Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (which ever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree (see figure 1 in Section 1.2 and definitions below).

6.2.5 Proximal Bronchial Tree

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram in Section 1.2. The following airways will be included according to standard anatomical relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

6.2.6 Whole Lung

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured. However, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

6.2.7 PTV Plus 2 cm

As part of the QA requirements for “low dose spillage” listed in 4.4.2 above, a maximum dose to any point 2 cm away in any direction is to be determined. To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning.

7.0 DOCUMENTATION REQUIREMENTS

7.1 Treatment Breaks

In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

8.0 COMPLIANCE CRITERIA

8.1 Dosimetry Compliance

Exceeding the critical organ dose limits by more than 2.5% constitutes a minor protocol violation. Exceeding these dose limits by more than 5% constitutes a major protocol violation.

8.2 Treatment Delivery Compliance

Set-up films will be compared to digitally reconstructed radiographs from the same beam's eye view. Deviations of less than 0.5 cm in the transverse plane and 1.0 cm in the cranio-caudal plane will be considered compliant. Deviations from 0.5-1.0 cm in the transverse plane and 1.0-1.25 cm in the craniocaudal plane will be considered minor protocol deviations. Deviations greater than those listed as minor will be considered major protocol deviations.

9.0 RADIATION TOXICITY

9.1 Radiation Pneumonitis

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically “geometric” corresponding to the radiation portal, but may also be ill defined. Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with non-steroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients. It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis prior to completing therapy, therapy should be put on hold until symptoms resolve. At that point, a clinical decision whether to finish therapy will be made by the treating physician.

9.2 Bronchial Injury

In the Indiana University phase I study published by Timmerman et al and subsequently by McGarry et al., the majority of patients treated at doses of 20 Gy times 3 fractions = 60 Gy or higher ultimately experienced atelectasis (collapse) of lung downstream from the area of treatment. This was felt to be related to injury of bronchi or bronchioles within or near the treated tumor. By unknown mechanisms over a period of 3-6 months, pulmonary parenchyma distal to the site of bronchial injury results in this focal lung collapse. In the majority of patients, this effect noted on imaging studies was asymptomatic. In others, the injury apparently correlated to a drop in diffusing capacity and arterial oxygen tension on pulmonary function tests. This process of collapse was not reversible in the Indiana University experience. This injury is the justification for reducing the dose per fraction in this protocol.

This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Since atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v. 3.0).

9.3 Other Significant Toxicity

If other severe toxicity resulting in withholding therapy is encountered, the details will be documented.

10.0 STUDY CALENDAR

Assessments	Pre-Study Entry	Each Day of Tx	6 Wks Post-Tx	12 Wks Post-Tx	Follow up
History/physical	X ^a		X	X	X ^h
Weight	X ^a		X	X	X ^h
Zubrod performance status	X ^a		X	X	X ^h
Evaluation by Thoracic Cancer Clinician	X ^b	X	X	X	X ^h
Pregnancy Test	X ^c				
Toxicity Evaluation ⁱ		X	X	X	X ^h
Chest X-ray (OPTIONAL)				X ^f	X ^f
CT scan (including liver and adrenals)	X ^{e,f}		X ^f		X ^f
PET scan (whole body)	X ^e				X ^g
Brain MRI or CT with contrast	X ^e				
PFTs ^d	X			X	X ⁱ

- A medical history, physical examination, weight, and assessment of Zubrod performance status must be completed within 4 weeks prior to study entry.
- Evaluation by an experienced thoracic cancer clinician should be performed within 8 weeks prior to study entry.
- For women of childbearing potential only, a serum or urine pregnancy test should be performed within 72 hours prior to start of protocol treatment.
- Includes routine spirometry, lung volumes and diffusion capacity; should be performed within 8 weeks prior to study entry.
- Should be performed within 45 days prior to study entry.
- CT scans should be done at 12 weeks and 6 months, and then every 3 months for the first 2 years and every 6 months for the next 2 years. CT scans may be alternated with chest X-ray (with initial CT scan done at first follow up visit) For the purposes of this protocol, a PET/CT may replace a CT of the chest, liver, and adrenal glands.
- Strongly encouraged; PET scans within 2 years post-treatment are required only if the criteria for local enlargement on CT is realized. The PET scan should occur within 3 months of the CT that defined local enlargement. Post-treatment PET scans done outside of the required criteria for assessment of local progression or after 2 years post-treatment may be done at the investigator's discretion but are not required.
- Follow-up evaluations (including toxicity evaluation, progress notes and physical, performance status assessment, and weight) should occur at week 12, followed by every 3 months for 1.5 years, then every 6 months for the next 2 years. If the patient is unavailable to come for follow up during these periods, or for patients who are not compliant with follow up appointments, "missed" imaging studies will be obtained at first available opportunity. Patients will be followed for a total of 4 years or until disease progression or death, whichever comes first. At minimum all patients in the Phase II portion of the study must be followed for survival for 2 years post treatment.
- Every 3 months for the first year. Use PFTs to monitor for signs of radiation pneumonitis (see Section 9.1).
- Adverse events grade 2 or higher shall be recorded on the toxicity record

11.0 DATA SUBMISSION SCHEDULE

Paper forms	Data Due
Original signed consent form	At least 24 hours prior to registration
Eligibility checklist	Prior to registration
Dose Level Accrual Tracking Spreadsheet	At the time of patient enrollment and each study visit
SBRT Treatment Planning Statistics	Upon treatment plan approval (completed by Dosimetry staff)
Toxicity Assessment Form	At each follow-up visit (Toxicity assessments during weekly treatment will be entered into IMPAC by PI)
QASM SAE Form	At the time of any SAE, to be reported according to institutional guidelines
SBRT Registration	At the time of enrollment
SBRT Treatment Record	Upon completion of treatment
SBRT Evaluation of Response	12 weeks post treatment
	Q 3 months for 2 years
SBRT Toxicity Record	At the time a study-related toxicity occurs
SBRT Off Treatment Record	At completion of treatment or at the time the patient goes off study
SBRT Follow-Up Form	12 weeks post treatment
	Every 3 months for first 1.5 years
	Every 6 months for following 2 years

12.0 CRITERIA FOR EVALUATION

12.1 Baseline documentation of “Target” and “Non-Target” Lesions

Patients enrolled to this protocol should have clinical stage I (T1 or T2, N0, M0) non-small cell lung cancer. At time of treatment, they should only have one site of gross disease in the lung with no metastases. The primary lung tumor should be identified as the **target lesion** and recorded and measured at baseline and with each follow-up imaging evaluation. The longest diameter (LD) for the *target lesion* will be calculated **from the treatment planning CT scan** using pulmonary windowing and reported as the baseline LD. The baseline LD will be used as reference by which to characterize the objective tumor. For follow-up assessment, diagnostic CT scans performed using a 5 mm contiguous reconstruction algorithm using pulmonary windowing taken as part of scheduled protocol follow-up are preferred as the method of evaluation for response. When CT scans are not available, chest x-ray determination will be allowed as long as the target lesion is clearly visible. Changes in serum tumor markers will not be allowed for assessment of either local tumor progression or metastatic progression.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases where it is indeterminate whether consolidation represents residual tumor or treatment effect, an FDG-PET scan may be used to determine the clinical suspicion of residual cancer. The FDG-PET should be interpreted with the original diagnostic FDG-PET. Lesions with a high suspicion of residual cancer should be biopsied.

All other lesions (or sites of disease) that appear after treatment (e.g., regional lymph nodes and distant metastases) should be identified as **non-target lesions** and should also be recorded at the point of their appearance and with each follow up. Non-target lesions should constitute measurable disease, which by definition requires having an appearance suspicious for carcinoma and having a dimension of at least 1.0 cm. Assessment of regional lymphatic or metastatic progression will be made in comparison to the required pretreatment staging studies or any other pretreatment imaging evaluations available. Only non-target lesions appearing at the margin of the PTV (i.e., within 1.0 cm) will have recorded measurements (see Marginal Failure in the table below). Recorded measurements of all other non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.2 Criteria for Removal from Protocol Treatment

All reasons for discontinuation of treatment must be documented. All patients will be followed until death for 4 years post-treatment or disease progression or death, whichever time point comes first. At minimum, all patients in the phase II portion of the study must be followed for survival for 2 years post treatment

- Disease progression at any time during therapy or the follow up period; the patient should be re-staged and sites of recurrence and/or progression documented. Re-biopsy is strongly encouraged.
- Grade 4 or 5 toxicity.
- The patient may elect to withdraw from study treatment at any time for any reason.
- Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow up.

13.0 ADVERSE EVENT REPORTING

13.1 Adverse Events (AEs)

Adverse events grade 2 or above will be tracked as described below; grade 1 events will not be collected.

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf).

Attribution (relatedness), Expectedness and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office of Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>.

13.2 Unanticipated Problems

Definition:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research; and
- Suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

13.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of

knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

13.4 Serious Noncompliance

Definition: noncompliance that materially increases risks, that result in substantial harm to subjects or others, or that materially, compromises the rights or welfare of participants.

13.5 Reporting to the Human Research Protection Office (HRPO) and the Quality Assurance and Safety Monitoring Committee (QASMC):

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study

These events must be reported to the IRB within 10 working days of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within 1 working day of the occurrence of the event or notification to the PI of the event.

13.6 Reporting of AE Information Following Study Completion

All SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time.

13.6.1 Follow Up Reports

Follow up reports are only required to be submitted if the new information changes the original assessment or indicates, in the light of new information, that there is an increased risk of harm to the participant or others.

13.7 SBRT Adverse Event Reporting

All acute and late adverse events from protocol radiation therapy will be reported and scored. Since the principal investigator is responsible for the

treatment and follow-up for each of these patients, he is responsible for reporting adverse events to the study coordinator. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be used to score adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page:

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf).

For purposes of this protocol, serious adverse events related to stereotactic radiation therapy include those listed as Grade 3-5 within the CTCAE document.

With respect to scoring dyspnea within the pulmonary toxicity criteria, an SAE will be scored if dyspnea meets grade 3 criteria AND is more severe than the baseline prior to treatment.

With respect to scoring FEV1 and DLCO as reported on pulmonary function tests, an SAE will be scored relative to the % change from baseline. Changes will be referenced to the baseline for a given patient (which will be abnormal for most patients), using a defined proportional decline. This scheme is depicted in the table below.

SBRT Pulmonary Toxicity Scale					
Grade					
Adverse Event	1	2	3	4	5
FEV-1 Decline	0.90-0.75 times patient's baseline value	<0.75-0.50 times patient's baseline value	<0.50-0.25 times patient's baseline value	<0.25 times patient's baseline value	Death
DLCO Decline	.90-0.75 times patient's baseline value	<0.75-0.50 times patient's baseline value	<0.50-0.25 times patient's baseline value	<0.25 times patient's baseline value	Death

13.8 Life-Threatening, Grade 4, and Grade 5 Events

All life-threatening events (events, which in view of the investigator, place the patient at immediate risk of death from the reaction) or Grade 4 or Grade 5 events that are definitely, possibly, or probably related to protocol treatment using radiation therapy must be reported to the Study Chair and study coordinator within 24 hours of discovery for up to 30 days following completion of treatment.

14.0 DATA AND SAFETY MONITORING

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date,

- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

15.0 STATISTICAL CONSIDERATIONS

15.1 Statistical Methods for Phase I Portion

15.1.1 Objective and Endpoint

The primary objective of Phase I is to estimate the rate of acute and late treatment-related grade 3 or 4 toxicity (per CTCAE, v.3.0) related to specific symptoms, including:

- Gastrointestinal: dysphagia, esophagitis, esophageal stricture, esophageal ulceration;
- Cardiac: pericarditis, pericardial effusion, cardiomyopathy, ventricular dysfunction;
- Hemorrhage: pulmonary or upper respiratory;
- Pulmonary: decline in pulmonary function as measured by pulmonary function tests, pneumonitis, pulmonary fibrosis, hypoxemia, pleural effusion
- Or any other grade 4 or 5 toxicity attributed to the therapy.

15.1.2 Dose Escalation Schema

In order to establish the maximum tolerated dose (MTD) of radiotherapy, in terms of Gy per fraction, that can be delivered using stereotactic body radiation therapy (SBRT) for central lung tumors, acceptable morbidity criteria must be defined. Since some of toxicities in the current study are life threatening, we hope to control the dose limiting toxicity (DLT: defined as a Grade 3 or Grade 4 non-hematologic toxicity) rate in a relatively low level. The design will take a “5+3” strategy rather than the conventional “3+3” design (see below).

This study consists of four escalating dose levels, only one of which will be open for accrual at any time. Dose Level A (9 Gy x 5 = 45 Gy; BED = 85.5 Gy*) will open first. Five (maximally eight) patients will be accrued to this dose level. After Dose Level A is closed, accrual will begin to Dose Level B (10 Gy x 5 = 50 Gy; BED = 100 Gy*). New dose levels cannot be opened until the preceding RT dose is deemed to be acceptable. At a given dose level, after 5 evaluable patients have been followed for a minimum of 90 days from the start of RT, these patients will be carefully evaluated with respect to treatment morbidity. Dose escalation will be determined as follows:

- If there are no acute dose limiting toxicities (DLTs: defined as a grade 3 or 4 non-hematologic toxicities) in the first 5 patients (0/5), then the current dose will be deemed to be acceptable and will be escalated.
- If there is 1 acute DLT observed in the first 5 patients (1/5), then an additional 3 patients will be recruited and followed for a minimum of 90 days. If there is 1 acute DLT observed (1/8), then the current dose will be deemed to be acceptable and will be escalated. If there are 2 or more acute DLTs observed ($\geq 2/8$), then the current dose will be deemed over-toxicity and the previous dose level will be considered as MTD for the Phase II trial (the study will be terminated if Level A is the current dose).
- If there are 2 or more acute DLTs observed in the first 5 patients ($\geq 2/5$), the current dose will be considered over-toxicity and the previous dose level will be considered as MTD for the Phase II trial (the study will be terminated if Level A is the current dose).
- However, the final decision for MTD will be based on a cohort of 8 patients and no re-escalation will be considered after “step-down” to the previous dosage level.
- If at any time a grade 5 toxicity (death) is observed, accrual will be suspended and the event will be reviewed by the Principal Investigator.
- This study is designed with 4 possible SBRT dose levels. If the 4th dose level is achieved, then the maximum sample size for this study is 32 patients. Nominally, such a “5+3” design will control the DLT around 12.5% level.
- After completing accrual to dose levels 2 and 3 (during the 3 month assessment window) accrual to the trial may continue at the previous ‘safe’ dose level. For example, if dose level 1 proves safe, patients can be accrued and treated at dose level 1 during the 3 month window of toxicity assessment between dose levels 2 and 3.

**BED = $nd(1 + d/\alpha/\beta)$, where n = number of fractions, d = dose per fraction, and $\alpha/\beta = 10$ for acute-reacting tissue*

15.2 Statistical Methods for Phase II Portion

15.2.1 Endpoints

The primary endpoint of Phase II is to estimate the local control rate at two years and the secondary endpoint of Phase II include the rates of local recurrence, regional recurrence, disease-free and overall survival at two years.

15.2.2 Study Design

This phase II study aims to improve the two-year local control rate from 60% to 80%, assuming that a control rate less than 60% is not of interest and that a 2-year control rate of 80% or more would definitely be of interest. Based on Fleming's single-stage design, 43 patients will be recruited during the phase II portion to detect such an improvement with 80% power and at a 2-sided Type I error rate of 0.05. However, the above sample size is a conservative estimate because it is based on Fisher's exact test for binary data. In the final analysis for local control rate, we will use survival data analysis (i.e., log-rank test) where more information (i.e., the exact times to local failures) will be utilized.

15.2.3 Data analysis

Unless otherwise noted, the efficacy analysis will be based on all patients who have completed the treatment and had primary efficacy measurements available while the safety analysis will be based on patients who received one or more fractions of SBRT.

Demographic and clinical characteristics of the sample, as well as response, toxicity by grade and loss to follow up will be summarized using descriptive statistics. Kaplan-Meier product limit estimator will be used to describe the distribution of local-failure free survival. The median time to local-failure and its 95% confidence interval will be estimated. The Kaplan-Meier product limit estimator will also be used to graphically describe progression free survival, overall survival as well as regional nodal recurrence-free survival. The proportion of patients who respond (completely or partially) will also be estimated and the corresponding 95% confidence intervals will be computed.

15.3 Monitoring the Study for Early Stopping Due to Unacceptable Toxicity

Early stopping of this trial will be based on unacceptable toxicity, defined as acute (within 90 days of the start of treatment) or late (more than 90 days from the start of treatment) grade 3 or 4 toxicity (per CTCAE, v.3.0) related to specific symptoms as detailed in Section 16.1 or any grade 4 or 5 toxicity attributed to the therapy. If a patient has more than one unacceptable toxicity, they will only be counted as one unacceptable toxicity for this analysis.

By assuming that a toxicity rate of 10% or less is acceptable and that a toxicity rate of 20% or more would definitely be unacceptable. Based on the sequential probability ratio test (SPRT) with 80% power and 0.05 significance level, the study will be halted if 4 of the first 4, or 5 of the first 11, or 6 of the first 18, or 7 of the first 25, or 8 of the first 32, or 9 of the first 39 patients experience unacceptable toxicities, or if the 10th unacceptable toxicity is observed before the last (43th) patient has completed the trial. If a grade 5 toxicity (death) is observed at any time, accrual will be suspended and the event will be reviewed by the study chair.

15.4 Accrual

The rate of accrual for the study is expected to be about 1 patient per month. It is expected that the accrual period of the study for phase I will be completed in approximately 36 months, depending on the DLT reached. Accrual for Phase II should be completed in 24 months. The whole study is anticipated to be finished in approximately 9 years.

15.5 Interim Analysis

An interim analysis will be conducted when 15 patients have at least 1-year follow-up. Because 10 patients from Phase I portion can be carried over to the Phase II, we anticipate that this will happen around the mid 2nd-year after the initiation of Phase II. If 10 or less local controls are observed out of these 15 patients, then the trial will be stopped because we will have 95% confidence that the “true” local control rate is no larger than 82%. Note that in the phase II setting, a trial usually will be stopped only because of futility. This trial will be continued even an overwhelming efficacy is observed in the interim analysis, and thus to have a more reliable estimation for the true treatment efficacy.

16.0 REFERENCES

1. Cancer facts and figures 2004. p. 4.
2. Shields TW. Surgical therapy for carcinoma of the lung. *Clin Chest Med* 1993;14:121-147.
3. Mountain CF. A new international staging system for lung cancer. *Chest* 1986;89:225S-233S.
4. Naruke T, Goya T, Tsuchiya R, *et al.* Prognosis and survival in resected lung carcinoma based on the new international staging system. *J Thorac Cardiovasc Surg* 1988;96:440-447.
5. Adebajo SA, Bowser AN, Moritz DM, *et al.* Impact of revised stage classification of lung cancer on survival: a military experience. *Chest* 1999;115:1507-1513.
6. McGarry RC, Song G, des Rosiers P, *et al.* Observation-only management of early stage, medically inoperable lung cancer: poor outcome. *Chest* 2002;121:1155-1158.
7. Coy P, Kennelly GM. The role of curative radiotherapy in the treatment of lung cancer. *Cancer* 1980;45:698-702.
8. Armstrong JG, Minsky BD. Radiation therapy for medically inoperable stage I and II non-small cell lung cancer. *Cancer Treat Rev* 1989;16:247-255.
9. Haffty BG, Goldberg NB, Gerstley J, *et al.* Results of radical radiation therapy in clinical stage I, technically operable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1988;15:69-73.
10. Kaskowitz L, Graham MV, Emami B, *et al.* Radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1993;27:517-523.
11. Dosoretz DE, Katin MJ, Blitzer PH, *et al.* Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. *Int J Radiat Oncol Biol Phys* 1992;24:3-9.
12. Dosoretz DE, Katin MJ, Blitzer PH, *et al.* Medically Inoperable Lung Carcinoma: The Role of Radiation Therapy. *Semin Radiat Oncol* 1996;6:98-104.
13. Sibley GS, Jamieson TA, Marks LB, *et al.* Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. *Int J Radiat Oncol Biol Phys* 1998;40:149-154.
14. Dosoretz DE, Galmarini D, Rubenstein JH, *et al.* Local control in medically inoperable lung cancer: an analysis of its importance in outcome and factors determining the probability of tumor eradication. *Int J Radiat Oncol Biol Phys* 1993;27:507-516.
15. Bradley JD, Wahab S, Lockett MA, *et al.* Elective nodal failures are uncommon in medically inoperable patients with Stage I non-small-cell lung carcinoma treated with limited radiotherapy fields. *Int J Radiat Oncol Biol Phys* 2003;56:342-347.
16. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995;60:615-622; discussion 622-613.
17. Curran WJ, Jr., Moldofsky PJ, Solin LJ. Analysis of the influence of elective nodal irradiation on postirradiation pulmonary function. *Cancer* 1990;65:2488-2493.
18. Krol AD, Aussems P, Noordijk EM, *et al.* Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? *Int J Radiat Oncol Biol Phys* 1996;34:297-302.
19. Williams TE, Thomas CR, Jr., Turrisi AT, 3rd. Counterpoint: better radiation treatment of non-small cell lung cancer using new techniques without elective nodal irradiation. *Semin Radiat Oncol* 2000;10:315-323.

20. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. *Radiother Oncol* 1996;41:41-44.
21. Robertson JM, Ten Haken RK, Hazuka MB, *et al.* Dose escalation for non-small cell lung cancer using conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1079-1085.
22. Bradley J, Graham MV, Winter K, *et al.* Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:318-328.
23. Lax I, Blomgren H, Naslund I, *et al.* Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994;33:677-683.
24. Blomgren H, Lax I, Naslund I, *et al.* Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol* 1995;34:861-870.
25. Blomgren H, *et al.* Radiosurgery for tumors in the body: Clinical experience using a new method. *J Radiosurg* 1998;1:63-74.
26. Timmerman R, Papiez L, McGarry R, *et al.* Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003;124:1946-1955.
27. McGarry RC, Papiez L, Williams M, *et al.* Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys* 2005;63:1010-1015.
28. Wulf J, Hadinger U, Oppitz U, *et al.* Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. *Radiother Oncol* 2000;57:225-236.
29. Negoro Y, Nagata Y, Aoki T, *et al.* The effectiveness of an immobilization device in conformal radiotherapy for lung tumor: reduction of respiratory tumor movement and evaluation of the daily setup accuracy. *Int J Radiat Oncol Biol Phys* 2001;50:889-898.
30. Cardenes HR, Timmerman R, Papiez L. Extracranial stereotactic radioablation: review of biological basis, technique and preliminary clinical experience. *Oncologia* 2002;23(4):193-199.
31. Timmerman R, Papiez L, McGarry R, *et al.* Extracranial stereotactic radioablation: Results of a phase I study in stage I non-small cell lung cancer. *Int J Rad Onc Bio Phys* 2003;57(2 Suppl):S280-281.
32. Onishi H, Araki T, Shirato H, *et al.* Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004;101:1623-1631.
33. Onishi H, Kuriyama K, Komiyama T, *et al.* Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: patient self-controlled breath-hold and beam switching using a combination of linear accelerator and CT scanner. *Lung Cancer* 2004;45:45-55.
34. Uematsu M, Shioda A, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666-670.
35. Wulf J, Hadinger U, Oppitz U, *et al.* Stereotactic radiotherapy of targets in the lung and liver. *Strahlenther Onkol* 2001;177:645-655.
36. Nagata Y, Negoro Y, Aoki T, *et al.* Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002;52:1041-1046.

37. Fukumoto S, Shirato H, Shimzu S, *et al.* Small-volume image-guided radiotherapy using hypofractionated, coplanar, and noncoplanar multiple fields for patients with inoperable Stage I nonsmall cell lung carcinomas. *Cancer* 2002;95:1546-1553.
38. Whyte RI, Crownover R, Murphy MJ, *et al.* Stereotactic radiosurgery for lung tumors: preliminary report of a phase I trial. *Ann Thorac Surg* 2003;75:1097-1101.
39. Uno T, Aruga T, Isobe K, *et al.* Radiation bronchitis in lung cancer patient treated with stereotactic radiation therapy. *Radiat Med* 2003;21:228-231.
40. Speiser BL, Spratling L. Remote afterloading brachytherapy for the local control of endobronchial carcinoma. *Int J Radiat Oncol Biol Phys* 1993;25:579-587.
41. Speiser BL, Spratling L. Radiation bronchitis and stenosis secondary to high dose rate endobronchial irradiation. *Int J Radiat Oncol Biol Phys* 1993;25:589-597.
42. Kelly JF, Delclos ME, Morice RC, *et al.* High-dose-rate endobronchial brachytherapy effectively palliates symptoms due to airway tumors: the 10-year M. D. Anderson cancer center experience. *Int J Radiat Oncol Biol Phys* 2000;48:697-702.
43. Celebioglu B, Gurkan OU, Erdogan S, *et al.* High dose rate endobronchial brachytherapy effectively palliates symptoms due to inoperable lung cancer. *Jpn J Clin Oncol* 2002;32:443-448.
44. Keall PJ, Kini VR, Vedam SS, *et al.* Potential radiotherapy improvements with respiratory gating. *Australas Phys Eng Sci Med* 2002;25:1-6.
45. Cheung PC, Sixel KE, Tirona R, *et al.* Reproducibility of lung tumor position and reduction of lung mass within the planning target volume using active breathing control (ABC). *Int J Radiat Oncol Biol Phys* 2003;57:1437-1442.